



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 7/20	A1	(11) International Publication Number: WO 93/04664 (43) International Publication Date: 18 March 1993 (18.03.93)
(21) International Application Number: PCT/US92/07409 (22) International Filing Date: 2 September 1992 (02.09.92) (30) Priority data: 755,149 5 September 1991 (05.09.91) US (71) Applicant: 7-L CORPORATION [US/US]; 25 East Poplar, Harrisburg, IL 62946 (US). (72) Inventor: DOUGLAS, Jerry, L. ; 25 East Poplar, Harrisburg, IL 62946 (US). (74) Agents: HEJLEK, Edward, J. et al.; Senniger, Powers, Leavitt & Roedel, One Metropolitan Square, 16th Floor, St. Louis, MO 63102 (US).		(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: MOUTHRINSE AND METHOD OF PREPARATION (57) Abstract A mouthrinse preparation having between about 0.25 % and about 0.65 % hydrogen peroxide, between about 0.005 % and about 0.1 % zinc chloride, at least about 0.012 % sodium citrate, at least about 0.03 % sodium lauryl sulfate, at least about 0.006 % citric acid and between about 2 % and about 3.5 % ethanol, the mouthrinse preparation remaining stable upon continuous exposure to a temperature of 37 °C at atmospheric pressure for at least 30 days. A method for preparation of same.		

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MOUTHRINSE AND METHOD OF PREPARATION

Background of the Invention

This invention is directed to a mouthrinse preparation for the purposes of oral therapy and the prevention of dental disease. More particularly, the invention is directed to a chemically stable mouthrinse composition which includes hydrogen peroxide and a method for preparation of such a mouthrinse.

Hydrogen peroxide and peroxide-containing preparations are known to be effective therapeutic and prophylactic treatments for caries, periodontal hemorrhaging, plaque, gingivitis, periodontitis, orthodontic appliance damage and other oral conditions. Frazier et al., U.S. Patent No. 4,980,152, disclose an oral preparation containing between 0.5% and 10% hydrogen peroxide.

Mouthrinses are known to contain numerous adjuvants in addition to hydrogen peroxide. Schiraldi et al., U.S. Patent No. 4,992,259, disclose the use of zinc compounds including zinc chloride as astringent-desensitizing agents.

Additionally, flavorings and colorings have been added to mouthrinses to improve their acceptability to the user. Surfactants have been added to enhance the bacterial activity of the mouthrinse. Anticoagulants have also been included to help the healing of hemorrhagic tissue.

Oral preparations containing such other ingredients in conjunction with hydrogen peroxide, however, have generally been unstable in storage, as the hydrogen peroxide reacts with one or more of the other ingredients in the preparation and components of the mouthrinse tend to precipitate. As a result, the capacity of the hydrogen

peroxide to release oxygen and of the other ingredients to perform their respective functions is lost or greatly diminished even after relatively short storage periods as, for example, on a drug store display shelf. Additionally, the instability of mouthrinses containing hydrogen peroxide has been known to render them unsatisfactory with respect to shelf-life requirements of the United States Food and Drug Administration.

Oral preparations also often contain relatively high concentrations of various alcohols for their effects of sterilizing, transporting and stabilizing. Asano et al., U.S. Patent No. 4,568,540, disclose oral preparations having at least 35% sorbitol. Commercially available mouthrinses often contain between about 15% and 30% alcohol.

Recently there has been increasing concern about the high alcohol content of commercially available mouthrinses. Scientific studies have linked the regular use of such mouthrinses to significant increases in the incidence of oral cancer. Additionally, there is a risk that alcoholic persons may intentionally ingest high alcohol mouthrinses, that children may incur serious injuries due to poisoning from high alcohol mouthrinses, and that adolescents may abuse such mouthrinses where liquor laws otherwise render alcohol unobtainable.

Summary of the Invention

Accordingly, it is an object of this invention to provide a chemically stable mouthrinse containing an amount of hydrogen peroxide which is effective for therapeutic and preventative oral treatment; it is a further object to provide a chemically stable mouthrinse containing an effective amount of hydrogen peroxide and having an acceptable taste and color; to provide a chemically stable mouthrinse which contains an effective amount of hydrogen

peroxide and meets United States Food and Drug Administration requirements regarding shelf life; to provide a chemically stable mouthrinse containing an effective amount of hydrogen peroxide and at least one additional antimicrobial agent; to provide a chemically stable mouthrinse containing an effective amount of hydrogen peroxide and a surfactant; to provide a chemically stable mouthrinse containing an effective amount of hydrogen peroxide and an anticoagulant; to provide a mouthrinse which has a low alcohol content.

Briefly, therefore, the present invention is directed to a mouthrinse preparation having between about 0.25% and about 0.65% hydrogen peroxide, between about 0.005% and about 0.1% zinc chloride, at least about 0.012% sodium citrate, the sodium citrate content being such that the ratio of sodium citrate to zinc chloride is in the range of from about 1 to 1 to about 2 to 1, at least about 0.03% sodium lauryl sulfate, the sodium lauryl sulfate content being such that the ratio of sodium lauryl sulfate to zinc chloride is in the range of from about 2 to 1 to about 8 to 1, at least about 0.006% citric acid and between about 2% and about 3.5% ethanol, said mouthrinse preparation having an acceptable shelf life.

The invention is also directed to a method for preparing a mouthrinse preparation involving the steps of providing a solution containing alcohol, preparing a zinc chloride solution by dissolving zinc chloride in deionized water and allowing the zinc chloride solution to cool, adding sodium lauryl sulfate, citric acid and sodium citrate to the zinc chloride solution, mixing the zinc chloride solution and allowing it to cool, mixing the alcohol solution with the zinc chloride solution and allowing a resulting solution to cool, and adding a hydrogen peroxide solution to the resulting solution and mixing to provide a mouthrinse.

Detailed Description

The present invention is directed to a mouthrinse composition for the purposes of oral therapy and the prevention of dental disease. More particularly, the invention is directed to a chemically stable mouthrinse composition which includes hydrogen peroxide. The invention is also directed to a method for the preparation of such a mouthrinse.

The mouthrinse composition of the present invention comprises an oxygen-releasing agent which also acts as an astringent and anti-inflammatory agent, specifically, hydrogen peroxide. Hydrogen peroxide helps prevent the accumulation and multiplication in the mouth of anaerobic bacteria generally associated with periodontal complications. The hydrogen peroxide has both a chemical effect as oxygen contacts the microbiota and a mechanical effect as the bubbling and foaming action of the peroxide upon swishing contact with saliva and oral tissue facilitates the delivery of active ingredients to affected areas. This chemical/mechanical action also facilitates the cleansing removal of microbiota, plaque, inflamed tissue and other local factors. Preferably, the mouthrinse comprises between about 0.25% and about 0.65% hydrogen peroxide (all percentages herein are on a weight/volume basis unless indicated otherwise). Hydrogen peroxide in amounts significantly less than about 0.25% would be insufficient to provide the desired therapeutic effect, whereas amounts significantly greater than about 0.65% would be potentially unstable under conditions of prolonged storage.

Zinc chloride is provided in the mouthrinse as an antimicrobial agent having an antiplaque effect. Zinc chloride advantageously has the ability to interfere with the metabolic activity of pathogenic microbiota. Zinc

chloride helps reduce gingival inflammation and restore edematous tissue to its normal state. The mouthrinse preferably comprises between about 0.005% and about 0.1% zinc chloride. Zinc chloride in amounts significantly less than about 0.005% would be insufficient to provide the desired therapeutic effect. A zinc chloride composition significantly greater than about 0.1% would make the mouthrinse unacceptably bitter in taste to be suitable for most normal human treatments. A significantly greater than normal microbiota population in the mouth of the host may indicate, or an unusually high tolerance for bitter taste may permit, the use of zinc chloride in amounts greater than about 0.1%.

The mouthrinse comprises sodium lauryl sulfate as a surfactant. Without being bound to any theory, it is believed that sodium lauryl sulfate serves to enhance the interaction among the mouthrinse, saliva and oral tissue. Additionally, sodium lauryl sulfate makes the cell walls of the microbiota more permeable, interferes with the metabolic processes of the microbiota, and enhances the ability of zinc chloride to interfere with the metabolic processes of the microbiota. The preferred mouthrinse composition comprises at least about 0.03% sodium lauryl sulfate. Although there is no critical maximum for sodium lauryl sulfate content, it is preferred to be provided in an amount such that the ratio of sodium lauryl sulfate to zinc chloride is in the range of from about 2 to 1 to about 8 to 1, most preferably about 4 to 1.

An anticoagulant to aid in the healing of hemorrhagic tissue is also provided in the mouthrinse. The preferred anticoagulant is sodium citrate, which also serves as an antimicrobial enhancer and an anti-inflammatory agent. Sodium citrate is provided in an amount of at least about 0.012% and up to about 0.2% or

greater. It is preferred that sodium citrate is provided in an amount such that the ratio of sodium citrate to zinc chloride is from about 1 to 1 to about 2 to 1.

Citric acid is provided in the mouthrinse for purposes of demineralization and stabilization. Citric acid is effective for adjusting and maintaining the pH of the mouthrinse in a range at which the hydrogen peroxide remains stable, roughly from about 3.5 to about 4.5. The citric acid content, which is substantially always greater than about 0.005%, is therefore that amount which is effective for achievement of the desired pH.

Any of a variety of pharmaceutically acceptable carrier media may be used including an aqueous alcohol. The presence of alcohol in the carrier provides sterilization capacity and is thought to influence product stability. The preferred carrier contains the denatured alcohol SD alcohol 38 B-2, which contains about 92% ethyl alcohol. It being an object of this invention to provide a low alcohol mouthrinse, it is preferred that the mouthrinse contain less than about 5% alcohol (mouthrinse total R-OH content) and, most preferably, less than about 3% alcohol.

The alcohol may be denatured with any of a variety of denaturing agents, alone or in combination, including, nonexclusively, anethole, anise oil, bay oil, bergamot oil, bitter almond oil, bubble-gum flavoring, cedar leaf oil, cinnamic aldehyde, cinnamon oil, clove oil, eucalyptol, eucalyptus oil, eugenol, lavender oil, menthol, peppermint oil, sassafras oil, spearmint oil, terpeneless spearmint oil, thyme oil, thymol and/or wintergreen oil. Generally, less than about 0.1% total denaturing agent is preferred in the mouthrinse. The preferred alcohol also contains Poloxamer 407 or another solubilizer to solubilize the denaturing agents. Generally, less than about 1.0 wt.% Poloxamer 407 is preferred.

In addition to the above-described components, the mouthrinse of the present invention may also contain glycerin, which is believed to serve as an additional surfactant. Glycerin may be present in the range of from
5 about 1.8% to about 9.0%.

The mouthrinse may also contain an appropriate chelating agent to keep the various minerals in combination. The preferred chelating agent is disodium EDTA provided in the range of from about 0.022% to about
10 0.1%.

Any of a number of pharmaceutically safe and compatible coloring agents, including, nonexclusively, D & C yellow #10 and D & C green #3, may also be used in effective amounts to enhance the acceptability of the
15 mouthrinse.

The mouthrinse of the invention may optionally contain any of a variety of sweetening agents alone or in combination. Sweetening agents may include, for example, saccharin, dextrose, levulose, and/or aspartame. Although
20 the sweetening agent content of the mouthrinse is variably dependent on the taste sought to be imparted and the strength of the selected sweetener, it is generally preferred that the sweetening agent content be less than about 2.5%.

25 In accordance with the method of the invention, the particular constituents of the mouthrinse, in quantities as described hereinabove, are mixed in the following manner. A 1% hydrogen peroxide solution is provided. This can be prepared by diluting a 3% hydrogen
30 peroxide solution with deionized water to a strength of about 1%.

An alcohol solution comprising ethanol, denaturing agents and a solubilizer is provided. This alcohol solution may be prepared by mixing its components until clear or may be obtained from any of numerous commercial suppliers.

A zinc chloride solution is prepared by dissolving the zinc chloride in deionized water and mixing until the solution is clear. To achieve a mouthrinse having stabilized hydrogen peroxide, the heat generated from this mixing process is allowed to dissipate prior to further processing of this zinc chloride solution.

A solution of remaining ingredients is prepared by dissolving the remaining mouthrinse components in deionized water. In the preferred embodiment, these components include sodium lauryl sulfate, citric acid, sodium citrate, glycerin, disodium EDTA, saccharin and the selected coloring agents.

The remaining ingredient solution is then mixed with the zinc chloride solution. The heat generated from the mixing process is allowed to dissipate prior to further processing.

As an alternative to preparing the above-described remaining ingredient solution and subsequently mixing it with the zinc chloride solution, these components may optionally be added directly to, and mixed with, the cooled zinc chloride solution. To achieve a mouthrinse having stabilized hydrogen peroxide, the heat generated from the mixing process is allowed to dissipate prior to further processing.

The alcohol solution is mixed with the solution comprising the zinc chloride and the remaining ingredients until it is substantially clear, except for the effect of any coloring agents present. To achieve a mouthrinse having stabilized hydrogen peroxide, the heat generated from this mixing process is allowed to dissipate prior to further processing.

The 1% hydrogen peroxide solution is then mixed with the solution comprising the zinc chloride, alcohol and remaining ingredients to provide the mouthrinse of the invention.

5 Mouthrinses prepared in accordance with the method of this invention are characterized by superior chemical stability and, consequently, shelf life. The mouthrinses are thus stable, i.e., they remain clear, with no visible formation of precipitates or detectable
10 evolution of gases after prolonged periods of storage, i.e., 30, 60, and 90 days of continuous exposure to temperatures of 37°C and normal atmospheric pressure.

The following examples illustrate the invention.

EXAMPLE 1

15 About 0.83 gallons of a 3% hydrogen peroxide solution was diluted with about 1.66 gallons of deionized water to provide a 1% hydrogen peroxide solution.

About 0.24 gallons of SD alcohol 38 B-2 comprising peppermint oil and spearmint oil denaturing
20 agents, Poloxamer 407 stabilizer, and about 92% ethyl alcohol was mixed with deionized water to a total volume of about 3.5 gallons and provided as an alcohol solution.

A zinc chloride solution was prepared by adding 0.0016 lbs. zinc chloride to deionized water to a total
25 volume of about 0.5 gallons and mixing until the solution was clear. The heat generated from the mixing process was allowed to dissipate.

A remaining ingredient solution was prepared by adding 0.2822 lbs. glycerin, 0.0044 lbs. disodium EDTA,
30 0.0024 sodium citrate, 0.00158 lbs. citric acid, 0.0022 lbs. sodium saccharin, 0.006 lbs. sodium lauryl sulfate, and D & C yellow #10 and D & C green #3 in effective amounts to a quantity of deionized water such that the total volume of the resulting solution was about 3.5
35 gallons.

The remaining ingredient solution was mixed with the zinc chloride solution. The heat generated from the mixing process was allowed to dissipate.

The alcohol solution was mixed with the solution containing the zinc chloride and remaining ingredients.

The 1% hydrogen peroxide solution was then added to the solution containing the alcohol, zinc chloride and remaining ingredients and mixed for several minutes to form a stabilized mouthrinse containing hydrogen peroxide.

10

EXAMPLE 2

A mouthrinse having the composition as set forth below was prepared by the method as set forth in Example 1.

	<u>Component</u>	<u>% (weight/volume)</u>
	D.I. water	93.85
15	Glycerin	2.822
	SDA38B2	2.388
	Poloxamer 407	0.398
	Sodium lauryl sulfate	0.06
20	Disodium EDTA	0.044
	Flavors	0.044
	Sodium citrate	0.024
	Sodium saccharin	0.022
	Zinc chloride	0.016
25	Hydrogen peroxide	0.595
	Citric acid	0.0158
	Coloring agents	Q.S.

The pH of the mouthrinse was 3.925; the specific gravity at 25°C was 1.0074.

EXAMPLE 3

Independent clinical studies, which included DNA probe analysis, were conducted using mouthrinses having the composition of Example 2 prepared in accordance with the method of the invention. The test results obtained from patients using the mouthrinse of the invention are presented in Tables I and II.

Table I

	Number of patients	117
10	% showing:	
	reduced inflammation	100
	reduced plaque	100
	reduced bleeding	98
	improved oral hygiene	100
15	Patient acceptance (%)	94

Table II

	Number of patients	20
	% showing:	
	reduced inflammation	100
20	reduced plaque	95
	reduced bleeding	100
	improved oral hygiene	100
	Patient acceptance (%)	100

EXAMPLE 4

Mouthrinses having the composition of Example 2 prepared in accordance with the method of the invention were independently evaluated for antimicrobial efficacy at the University of Iowa Dows Institute for Dental Research. The tests involved a spectrum of microorganisms

representing odontopathogens associated with different oral diseases. The mouthrinse was found to be antibacterially effective against all the test organisms. Various minimum inhibitory concentrations (MIC) of the mouthrinse were
5 tested in each instance. Even mouthrinse diluted substantially in distilled water killed the tested pathogens and/or inhibited their growth.

Efficacy was evaluated using a spectrophotometer to measure the turbidity, in terms of absorbance of 660 nm
10 wavelength light, of in vitro bacterial samples exposed to the mouthrinse of the invention. A lack of absorbance/turbidity corresponds to positive microbiocidal activity. As shown in Fig. 1, three representative oral streptococci were susceptible, even with the mouthrinse
15 diluted out to 8 and to 32 fold. Fig. 2 illustrates the efficacy of the mouthrinse against selected periodontal pathogens. Fig. 3 illustrates the efficacy of the mouthrinse against other selected microorganisms, two of which, S. marcescens and C. albicans, may be associated with
20 dangerous oral infections in immunocompromised patients. A. viscosus has been associated with gingivitis and root surface caries. Figs. 4-9 illustrate the rate of killing of representative microorganisms by the mouthrinse. The logarithm of colony forming units per milliliter of test
25 suspension (cfu/ml) is plotted versus time. A decrease in the number of colony forming units corresponds to positive microbiocidal activity. A. actinomycetemcomitans of Fig. 9 is considered to be a serious odontopathogen and may be associated with localized juvenile periodontitis.

30

EXAMPLE 5

Mouthrinse having the composition of Example 2 prepared in accordance with the method of the invention was subjected to accelerated testing techniques by being held

continuously at 37°C and atmospheric pressure. After 30, 60 and 90 day intervals, the mouthrinse was stable in that the components of the mouthrinse were retained in solution with no significant evolution of gases. The mouthrinse
5 remained clear, with no visible formation of precipitates. Under these test conditions, each thirty days of continuous exposure is estimated to correspond to one full year of shelf life.

In view of the above, it will be seen that the
10 several objects of the invention are achieved.

Although specific examples of the present invention and its application are set forth herein, it is not intended that they are exhaustive or limiting of the invention. These illustrations and explanations are
15 intended to acquaint others skilled in the art with the invention, its principles, and its practical application, so that others skilled in the art may adapt and apply the invention in its numerous forms, as may be best suited to the requirements of a particular use.

CLAIMS

1. A mouthrinse preparation comprising between about 0.25% and about 0.65% hydrogen peroxide, between about 0.005% and about 0.1% zinc chloride, at least about 0.012% sodium citrate, at least about 0.03% sodium lauryl sulfate, at least about 0.006% citric acid and between
5 about 2% and about 3.5% ethanol, said mouthrinse preparation remaining stable upon continuous exposure to a temperature of 37°C at atmospheric pressure for at least 30 days.

2. A mouthrinse preparation as set forth in claim 1, said mouthrinse preparation remaining stable upon continuous exposure to a temperature of 37°C at atmospheric pressure for at least 60 days.

3. A mouthrinse preparation as set forth in claim 1, said mouthrinse preparation remaining stable upon continuous exposure to a temperature of 37°C at atmospheric pressure for at least 90 days.

4. A mouthrinse preparation as set forth in claim 1 comprising between about 2% and about 2.5% ethanol.

5. A mouthrinse preparation as set forth in claim 1 wherein the sodium citrate content is such that the ratio of sodium citrate to zinc chloride is in the range of from about 1 to 1 to about 2 to 1 and the sodium lauryl sulfate content is such that the ratio of sodium lauryl sulfate to zinc chloride is in the range of from about 2 to
5 1 to about 8 to 1.

6. A mouthrinse preparation as set forth in claim 1 additionally comprising a denaturing agent selected from the group of denaturing agents comprising anethole, anise oil, bay oil, bergamot oil, bitter almond oil, 5 bubble-gum flavoring, cedar leaf oil, cinnamic aldehyde, cinnamon oil, clove oil, eucalyptol, eucalyptus oil, eugenol, lavender oil, menthol, peppermint oil, sassafras oil, spearmint oil, terpeneless spearmint oil, thyme oil, thymol and wintergreen oil.

7. A mouthrinse preparation as set forth in claim 5 additionally comprising a solubilizer.

8. A mouthrinse preparation as set forth in claim 7 wherein said solubilizer is poloxamer 407.

9. A mouthrinse preparation as set forth in claim 1 additionally comprising a surfactant.

10. A mouthrinse preparation as set forth in claim 9 wherein said surfactant is glycerin.

11. A mouthrinse preparation as set forth in claim 10 comprising between about 1.8% and about 9.0% glycerin.

12. A mouthrinse preparation as set forth in claim 1 additionally comprising a chelating agent.

13. A mouthrinse preparation as set forth in claim 12 wherein said chelating agent is disodium EDTA and constitutes between about 0.22% and about 0.1% disodium EDTA.

14. A mouthrinse preparation as set forth in claim 1 additionally comprising a coloring agent.

15. A mouthrinse preparation as set forth in claim 1 additionally comprising a sweetening agent.

16. A mouthrinse preparation consisting of between about 0.25% and about 0.65% hydrogen peroxide, between about 0.005% and about 0.1% zinc chloride, at least about 0.012% sodium citrate, the sodium citrate content
5 being such that the ratio of sodium citrate to zinc chloride is in the range of from about 1 to 1 to about 2 to 1, at least about 0.03% sodium lauryl sulfate, the sodium lauryl sulfate content being such that the ratio of sodium lauryl sulfate to zinc chloride is in the range of from
10 about 2 to 1 to about 8 to 1, at least about 0.006% citric acid, between about 2% and about 3.5% ethanol, less than about 0.1% denaturing agent or combination of denaturing agents, between about 1.8% and about 9.0% glycerin, between about 0.022% and about 0.1% disodium EDTA, less than about
15 1.0% solubilizer, less than about 1.0% sweetening agent or combination of sweetening agents, and the balance of deionized water, said mouthrinse preparation having a shelf life of greater than about 2 years.

17. A mouthrinse preparation consisting essentially of between about 0.25% and about 0.65% hydrogen peroxide, between about 0.005% and about 0.1% zinc chloride, at least about 0.012% sodium citrate, the sodium
5 citrate content being such that the ratio of sodium citrate to zinc chloride is in the range of from about 1 to 1 to about 2 to 1 on a weight percent basis, at least about 0.03% sodium lauryl sulfate, the sodium lauryl sulfate content being such that the ratio of sodium lauryl sulfate

10 to zinc chloride is in the range of from about 2 to 1 to
about 8 to 1 on a weight percent basis, at least about
0.006% citric acid, between about 2% and about 3.5%
ethanol, less than about 0.1% denaturing agent or
combination of denaturing agents, between about 1.8% and
15 about 9.0% glycerin, between about 0.022% and about 0.1%
disodium EDTA, less than about 1.0% solubilizer, less than
about 1.0% sweetening agent or combination of sweetening
agents, and the balance of deionized water, said mouthrinse
preparation having a shelf life of greater than about 2
20 years.

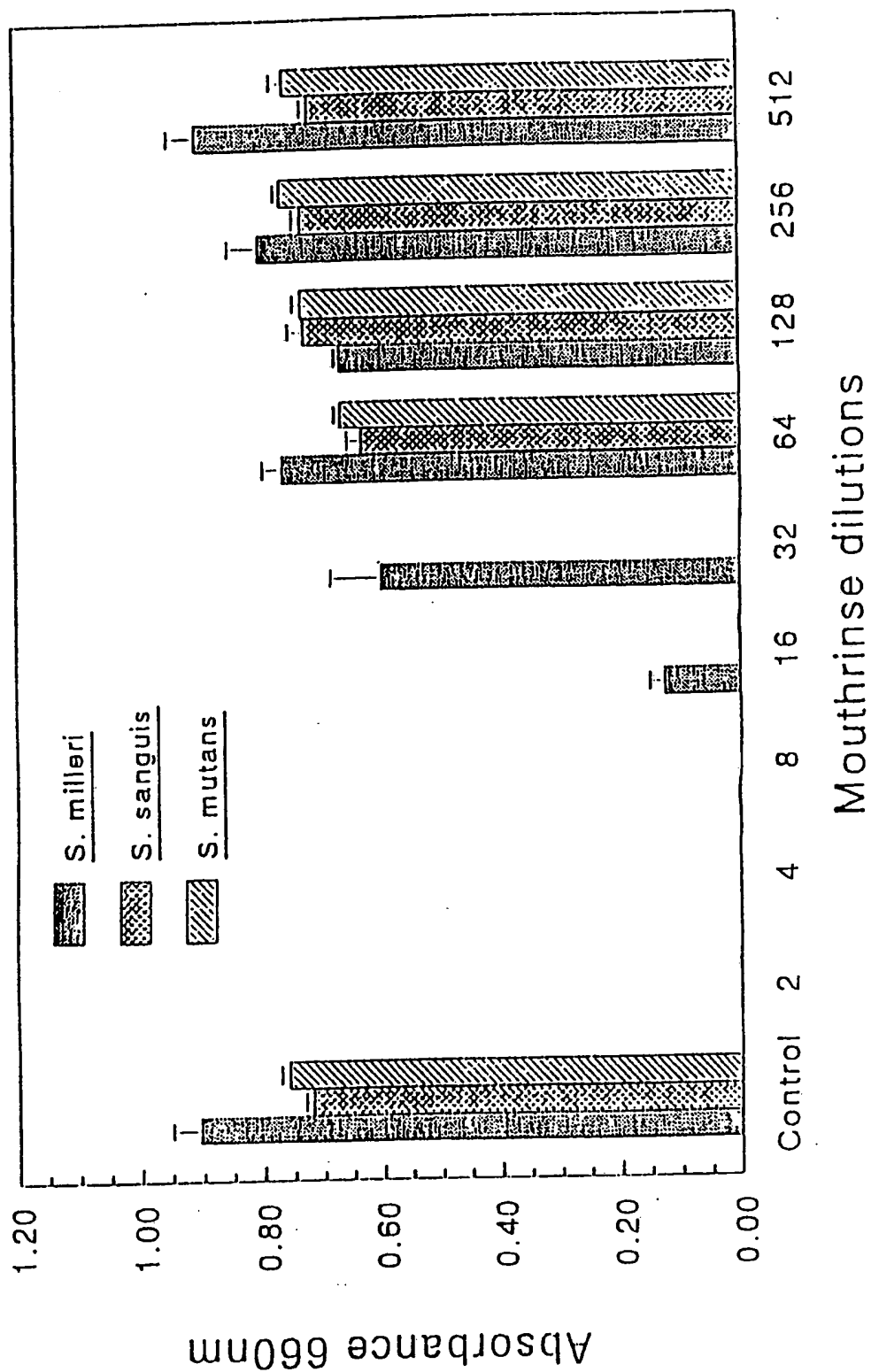
18. A method for preparing a mouthrinse
preparation comprising the steps of:

providing an alcohol solution containing alcohol;
preparing a zinc chloride solution by dissolving
5 zinc chloride in deionized water and allowing the zinc
chloride solution to cool;
adding sodium lauryl sulfate, citric acid and
sodium citrate to the zinc chloride solution, mixing the
zinc chloride solution, and allowing the zinc chloride
10 solution to cool;
mixing the alcohol solution with the zinc
chloride solution and allowing a resulting solution to
cool; and
adding a hydrogen peroxide solution to the
15 resulting solution and mixing to provide said mouthrinse.

19. A mouthrinse preparation prepared by the
method of claim 18.

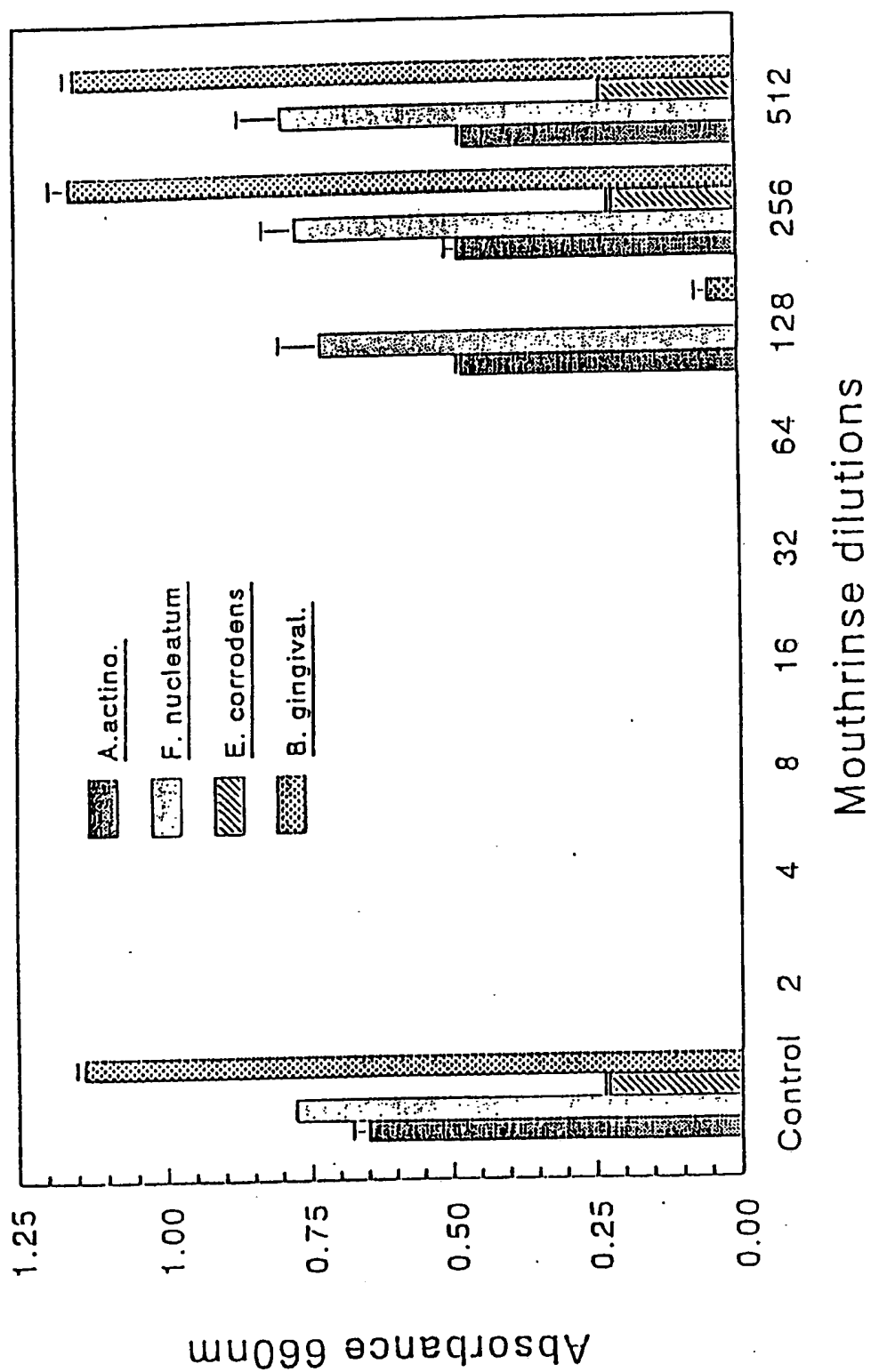
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Fig. 1



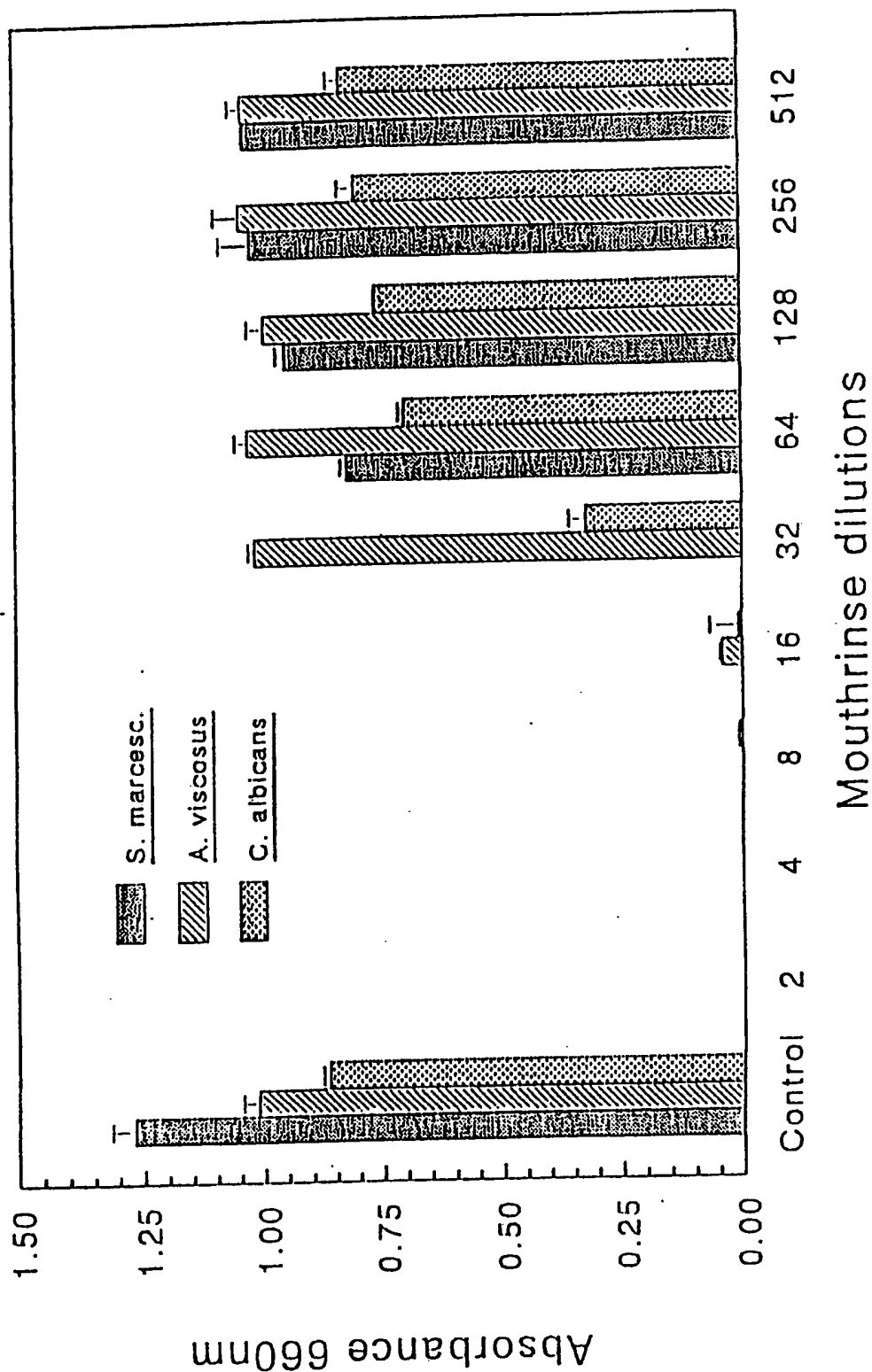
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Fig. 2



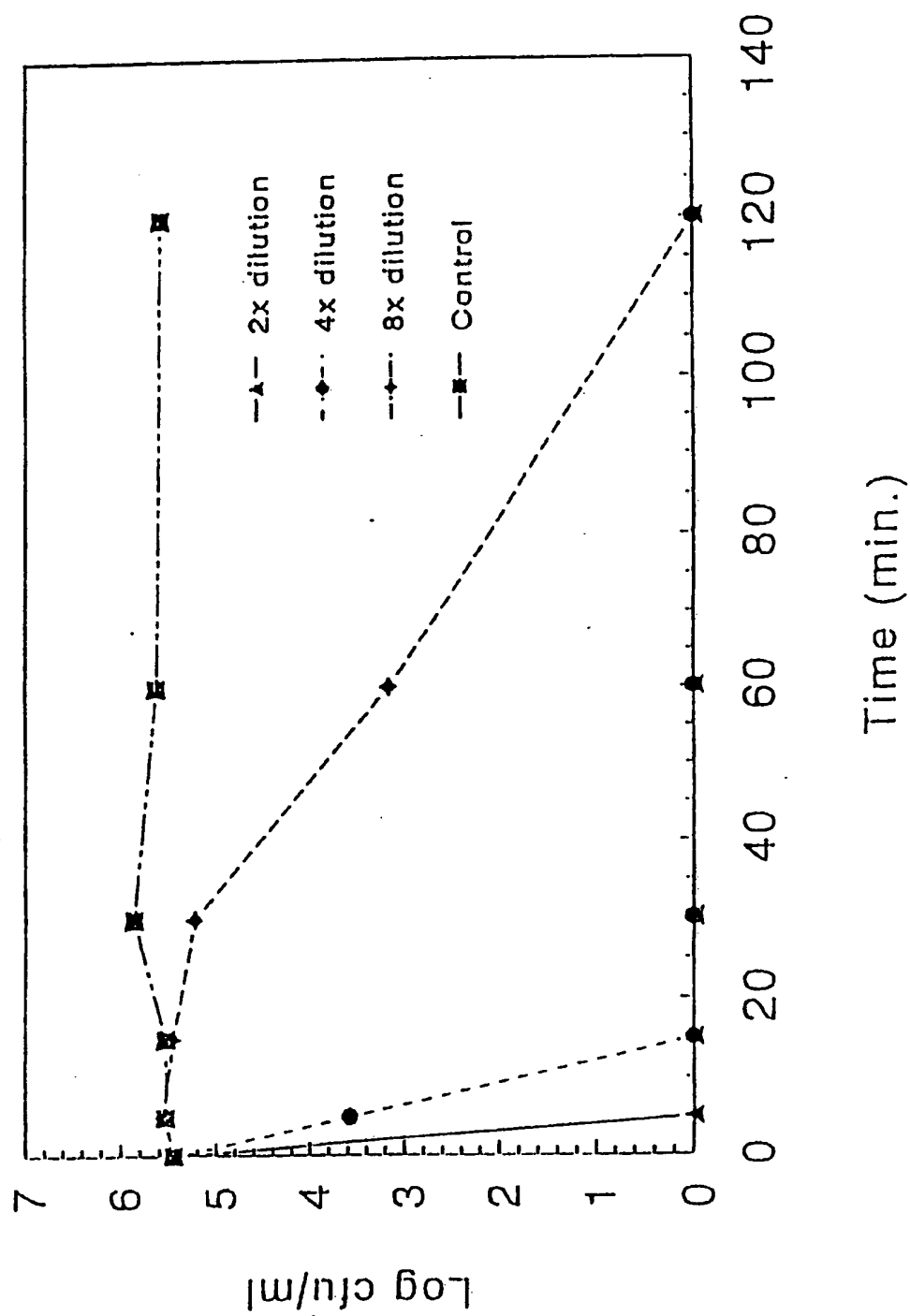
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Fig. 3



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Fig. 4



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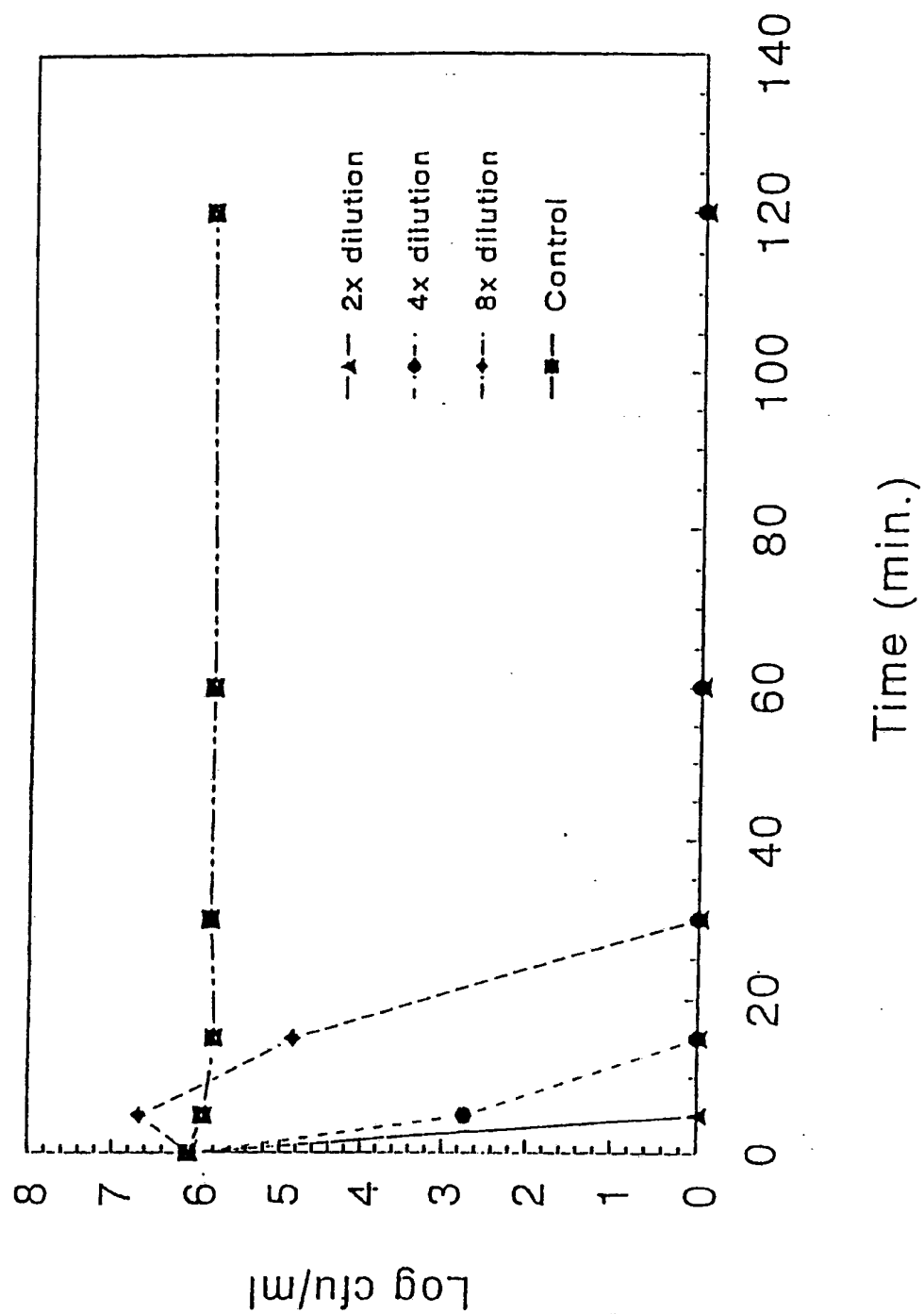


Fig. 5

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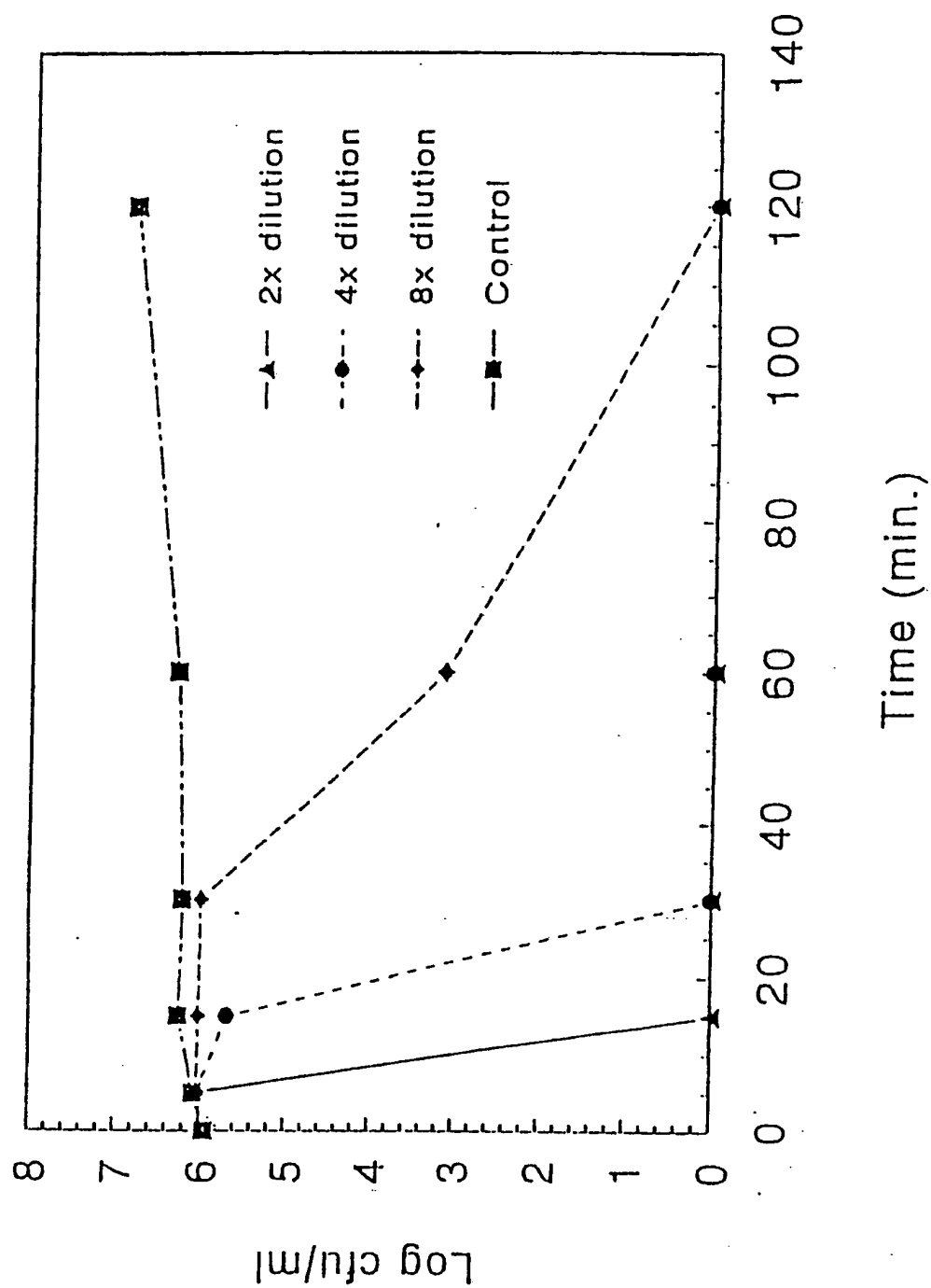


Fig. 6

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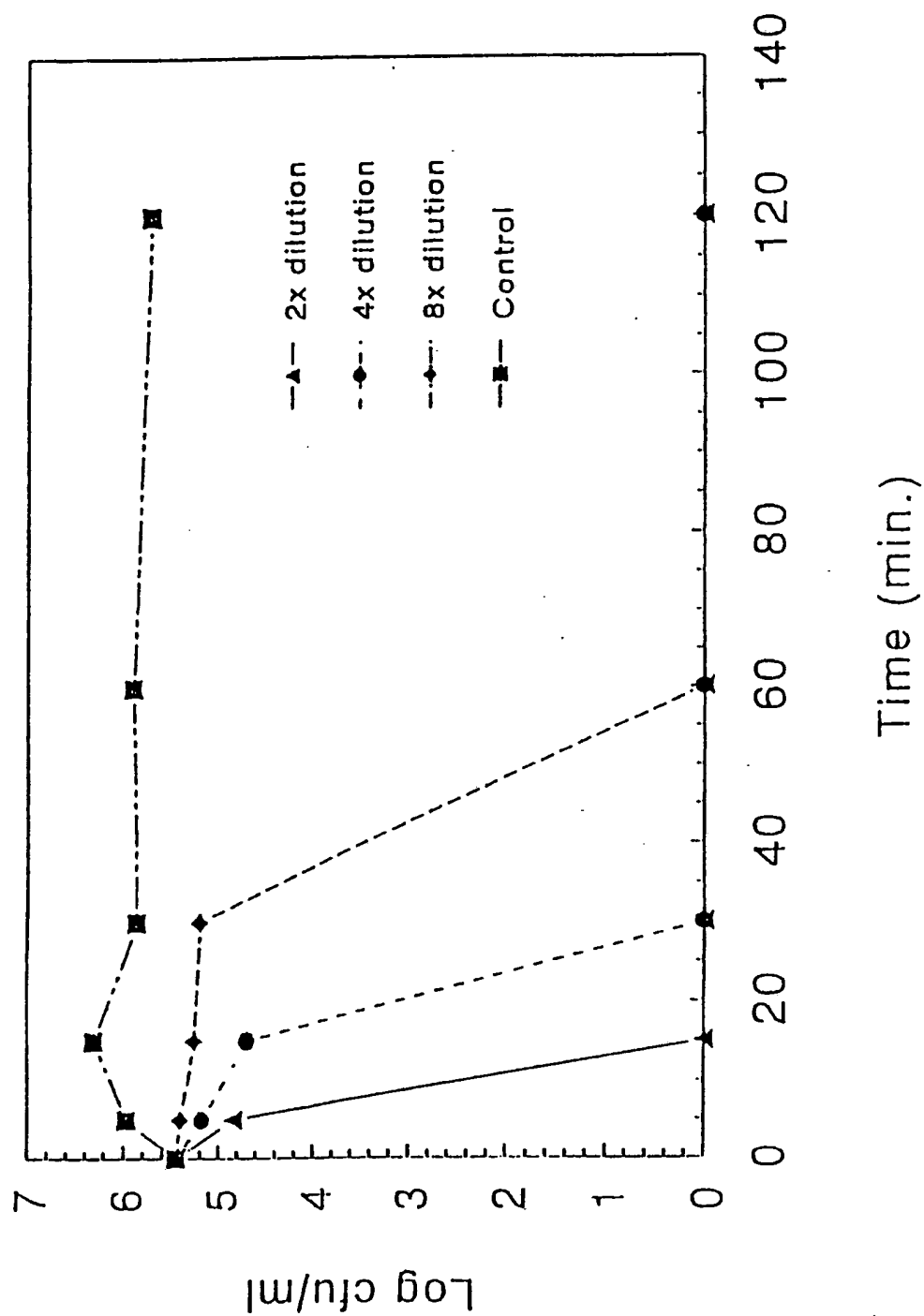


Fig. 7

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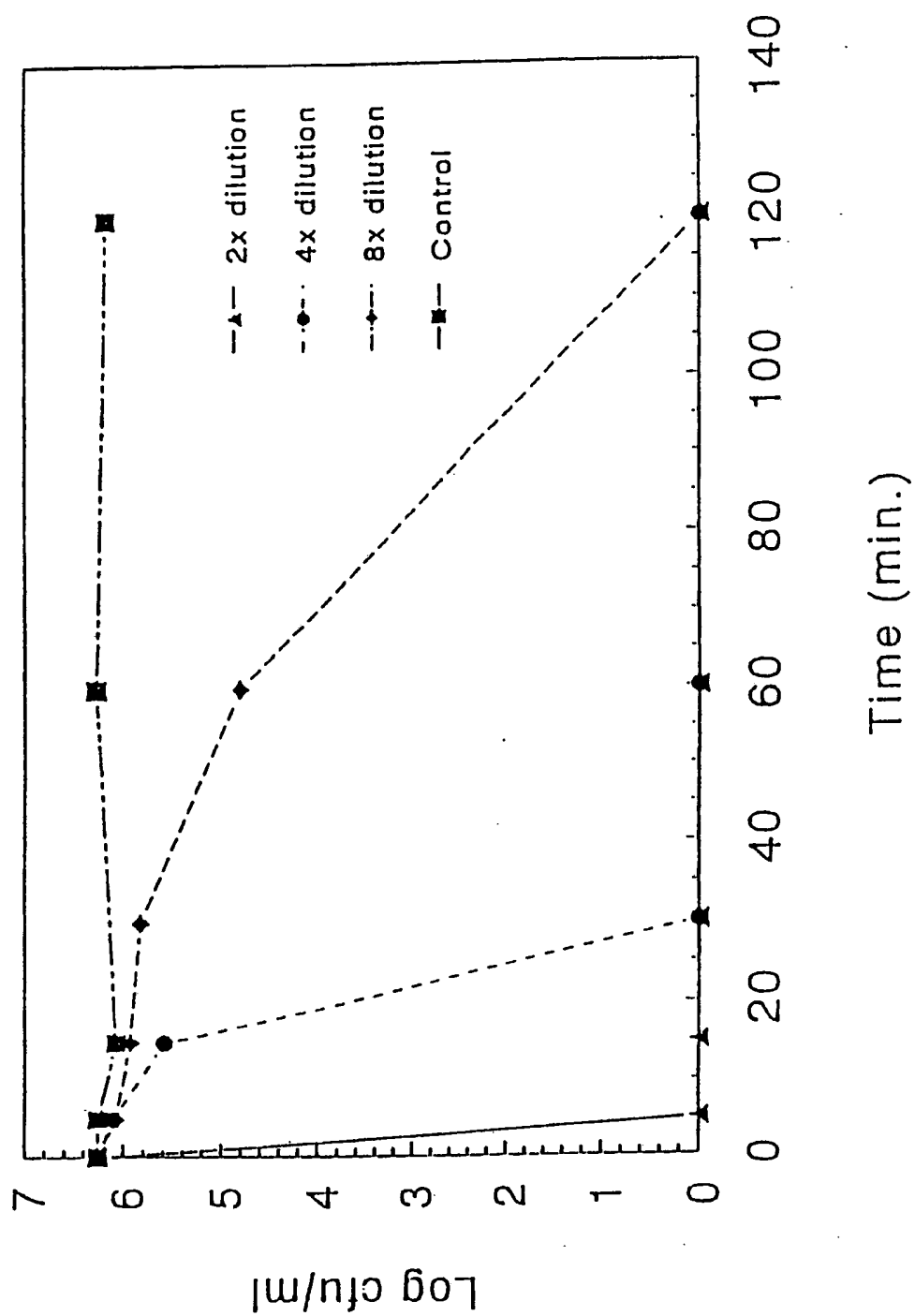


Fig. 8

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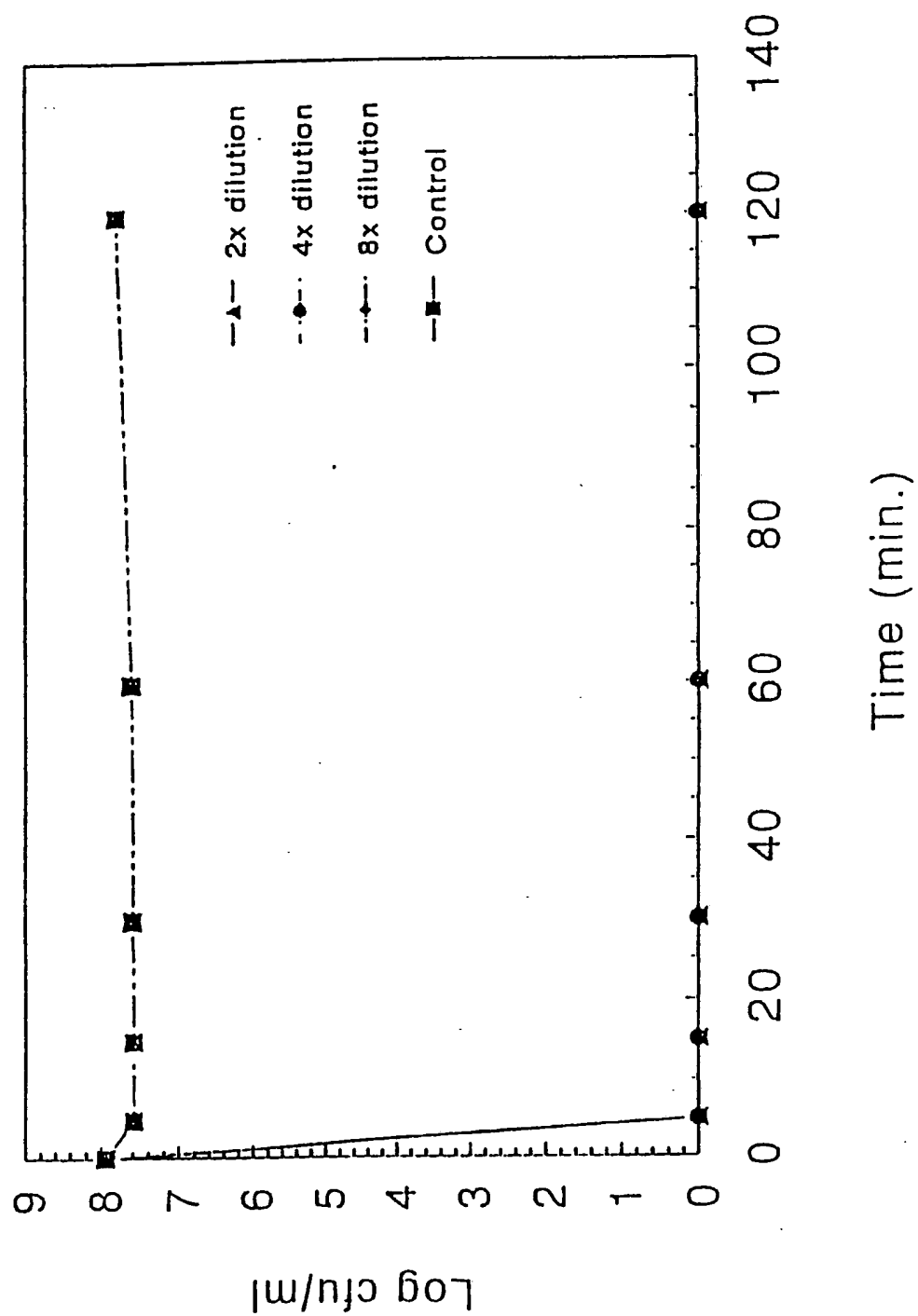


Fig. 9

INTERNATIONAL SEARCH REPORT

PCT/US92/07409

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 7/20

US CL :424/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/53

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	US,A, 5,104,644 (DOUGLAS) 14 APRIL 1992 See entire document	1 to 19
A	US,A, 5,035,882 (HUSSEIN ET AL) 30 JULY 1991 See entire document	1 to 19
A	US,A, 4,992,259 (SCHIRALDI) 12 FEBRUARY 1991 See entire document	1 to 19
A	US,A, 4,980,152 (FRAZIER ET AL) 25 DECEMBER 1990 See entire document	1 to 19

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Date of the actual completion of the international search	Date of mailing of the international search report
09 DECEMBER 1992	11 JAN 1993

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/07409

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 4,961,923 (HEYDE) 09 OCTOBER 1990 See entire document	1 to 19
A	US,A, 4,550,018 (AMBIKE ET AL) 29 OCTOBER 1985 See entire document	1 to 19